UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

SM

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,535	07/10/2000	George L. Murphy	AMBI:055US/MBW	9527

7590 02/25/2004

FULBRIGHT & JAWORSKI L.L.P.
SUITE 2400
600 CONGRESS AVENUE
AUSTN, TX 78701

EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,535	MURPHY ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

S.A.M.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-19 and 21-57* is/are pending in the application.

4a) Of the above claim(s) *49-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 11-19, 21-48 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to Applicants' response, filed on November 3, 2003. Currently, claims 1-7, 9, 11-19 and 21-57 are pending; claims 1-7, 9, 11-19, 21-48 and 53-57 have been examined on the merits and are rejected herein, and claims 49-52 have been withdrawn.

2. This action contains new rejections, necessitated by Applicants' amendment, and therefore, this action is made FINAL. Specifically, for example, Claim 9 has been amended to require "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative". Any rejections not reiterated herein are hereby withdrawn.

Claim Objections

3. Claim 11 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Short et al. (WO 98/01581, cited in the IDS).

Short teaches a method creating a nucleic acid comprising;

a) annealing a defined primer nucleic acid to at least one template nucleic acid;

b) performing a first extension by extending the primer nucleic acid employing the template nucleic acid to form an extended nucleic acid;

c) denaturing the extended nucleic acid from the template nucleic acid;

d) annealing the extended nucleic acid to at least a second template nucleic acid;

e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

f) adding at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, before or during at least one of the first or second extension, wherein said dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative agent is incorporated into said extended nucleic acid (see pages 7-9 and 67).

With respect to the limitation of "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative", Short teaches the use of DNA adducts, DNA intercalating agents, DNA binding proteins, triple helix forming agents, competing transcription polymerase, chain terminators, and polymerase inhibitors or poisons, which are considered to encompass the recitation of "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative" (see pages 8 and 67). Specifically, Short teaches numerous examples of DNA adducts, for example, (including those with an "alkaline condition") which

block or interrupt the amplification process (see page 8). The specification defines "analog" as "a molecule that may *or may not* structurally resemble a naturally occurring molecule, but functions similarly to the naturally occurring molecule". See page 23, lines 6-8. In the instant case, the DNA adducts, for example, may not structurally resemble a dideoxynucleotide, but functions similarly to the dideoxynucleotide, as it functions to block or interrupt amplification. Furthermore, Short teaches the use of nucleotide analogs (including at least one ribonucleotide, e.g., 5-bromouracil) that can also be used to block or interrupt amplification (see pages 33-34 and 67). Again, even if these analogs are structurally different, they function similarly to dideoxynucleotides. Additionally, "derivative" is defined as "a chemically modified or altered form of a naturally occurring molecule". (see page 23, lines 5-6) Therefore, because the DNA adducts and nucleotide analogs, for example, are "a chemically modified or altered form of" a dideoxynucleotide, they are considered to be dideoxynucleotide derivatives. Finally, Short teaches that chain terminators are used to block or interrupt polynucleotide synthesis or amplification (see page 67). Dideoxynucleotides are considered to be (and therefore an inherent property of) "chain terminators". See, for example, Rosenthal et al. (USPN 6,087,095, col. 5, lines 38-54, previously cited), and Monforte et al. (USPN 5,830,655, col. 9, lines 39-40 and col. 35, line 39) who teach that dideoxynucleotides are chain terminators.

The reference is directed to producing polynucleotides by interrupting polynucleotide synthesis using a chain terminator, followed by specific, self-primed primer extension (see pgs. 7 and 67). The first step, interrupting polynucleotide synthesis, encompasses both random and non-random primer extension because Short does not limit the polynucleotide synthesis to only random amplification (see pgs. 7 and 67). During the interrupting step, fragments of different

length of the polynucleotide are being generated, creating "resultant polynucleotides" (pg. 7). Following the interrupting step, single or double stranded polynucleotides are added to the resultant polynucleotide fragments, wherein the added polynucleotides comprise an "area of identity in an area of heterology" to one or more of the resultant polynucleotide fragments (i.e., these added polynucleotides are of a defined sequence, and will anneal to a defined region) (pg. 7). Following the annealing of the defined polynucleotides (i.e., defined primer), the polynucleotides are incubated, thus performing linear primer extension.

Thus, Short teaches that the addition of a chain terminator occurs **before** the annealing of a defined primer nucleic acid to at least one first template nucleic acid. However, it is also inherent that while some of the added polynucleotides (i.e., defined primers) are annealing to some resultant polynucleotides, some of the resultant polynucleotides are simultaneously are still being generated addition of chain terminators. That is, since some of the resultant fragments will be small, they will be generated more quickly, and therefore, will begin annealing to the added polynucleotides, while some of the larger resultant fragments are still being generated interrupted by the chain terminators. Thus, Short also teaches that the addition of the chain terminator also occurs **during** the at least one of the first extensions.

It is also noted that steps c)-e) can be occur a plurality of times to produce a polynucleotide that encodes a protein of interest (pgs. 6-7). The reference also teaches the various possibilities of the polynucleotides (e.g. lengths of polynucleotides) used, amplification conditions, etc. (pgs. 27-35). The reference also teaches polynucleotide synthesis can be interrupted by polymerase inhibitors, DNA binding proteins, etc. (pg. 67). Furthermore, the reference teaches that if further processing of the resultant polynucleotides is desired, DNA

adducts (and thus, any of the agents added interrupted polynucleotide synthesis) must be removed (pg. 8).

Applicants' Arguments

Applicants' argue Short does not teach defined primers or adding at least one at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative (see pages 13-16 of Applicants' response. Specifically, Applicants' allege Short teaches random primers or "at best, Short teaches primers generically". (see page 14 of Applicants' response) Furthermore, Applicants' allege Short does not teach the addition of at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative or that these agents are incorporated into the extended nucleic acid.

Response to Applicants' Arguments

Applicants' arguments have been considered, but are not persuasive for several reasons. First, there does not appear to a specific definition of "defined" primers in the specification, and therefore this recitation has been interpreted broadly, as to encompass any primer. The express definition of "primers" contained on page 26, lines 21-23, states, "The term 'primer nucleic acid' or 'primer' is meant to encompass *any* nucleic acid that *may* anneal to a template nucleic acid, thereby initiating the synthesis of a nascent nucleic acid from the end of the primer." As Applicant acknowledges, Short teaches primers that would meet this definition. Furthermore, it is also noted that Short does not limit his teachings to using "undefined" primers. For example, on page 34, line 28 to page 35, line 3; page 38, lines 10-15; page 39, lines 3-6; page 41, lines 25-28; page 47, lines 6-20, teach incorporating specific nucleic acids into the primers for use in extending particular templates. It is also noted, the claims use of the recitations "first extension"

is relative, and therefore, a "first" extension reaction can be considered to be the first specific, self-primed primer extension (see above). With respect to Applicants' arguments regarding "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative", Short teaches the addition of these agents (see rejection above). These agents (e.g., dideoxynucleotides and dideoxynucleotide analogs, such as 5-bromouracil, 2-aminopurine, etc.) would be incorporated into the extended nucleic acid, since they are included in the extension reaction. Accordingly, the rejection is maintained.

6. Claims 1-7, 9, 11-19, 21-41, 43-44, 46-47, 53-55 and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by Volkov (USPN 6,534,292).

Volkov teaches a method creating a nucleic acid comprising;

a) annealing a defined primer nucleic acid to at least one template nucleic acid;

b) performing a first extension by extending the primer nucleic acid employing the template nucleic acid to form an extended nucleic acid;

c) denaturing the extended nucleic acid from the template nucleic acid;

d) annealing the extended nucleic acid to at least a second template nucleic acid;

e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

f) adding at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, before or during at least one of the first or second extension, wherein said dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative agent is incorporated into said extended nucleic acid (see col. 1, lines 56-67; col. 2, lines 1-12

and 37-62; col. 4, lines 9-34; col. 5, line 60 to col. 6, line 8; col. 6, lines 34-40 and 48-67; cols. 7-8; col. 9, lines 24-43; and cols. 23-24).

Volkov also teaches the removal of nucleotides using Exonuclease III (col. 5, lines 14-18), using length-altering agents comprising alkaline treatment (col. 5, lines 3-6), the template can be any type of nucleic acid, nucleic acid analog or nucleic acid derivative (col. 2, lines 48-67), the template can be various sizes (col. 6, lines 16-20), and the extended fragments can be of varying sizes and sequences (col. 4, line 21 to col. 7, line 43).

7. Claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative obvious under 35 U.S.C. 103 over Stemmer, W. (USPN 6,506,603).

Stemmer teaches a method creating a nucleic acid comprising;

a) annealing a defined primer nucleic acid to at least one template nucleic acid;

b) performing a first extension by extending the primer nucleic acid employing the template nucleic acid to form an extended nucleic acid;

c) denaturing the extended nucleic acid from the template nucleic acid;

d) annealing the extended nucleic acid to at least a second template nucleic acid;

e) performing a second extension by extending the extended nucleic acid employing the second template nucleic acid to form a twice extended nucleic acid;

f) adding at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, before or during at least one of the first or second extension, wherein said dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative

agent is incorporated into said extended nucleic acid (see cols. 4, 6, 22-23, 25-31, and cols. 123-130).

With respect to the limitation of "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative", Stemmer teaches the use of chemical mutagens, intercalating agents, polymerases and nucleotide analogs, which are considered to encompass the recitation of "at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative" (see col. 123, lines 45-66, for example). Specifically, these agents cause incomplete extensions (see col. 123, lines 45-66, and col. 31, lines 40-62, for example). The specification defines "analog" as "a molecule that may *or may not* structurally resemble a naturally occurring molecule, but functions similarly to the naturally occurring molecule". See page 23, lines 6-8. In the instant case, the above agents may not structurally resemble a dideoxynucleotide, but functions similarly to the dideoxynucleotide, as it functions to create incomplete extension products. Furthermore, Stemmer teaches using nucleotide analogs (including at least one ribonucleotide, e.g., 5-bromouracil) that can also be used to create incomplete extension products (see col. 27). Again, even if these analogs are structurally different, they function similarly to dideoxynucleotides. Additionally, "derivative" is defined as "a chemically modified or altered form of a naturally occurring molecule". (see page 23, lines 5-6) Therefore, because the above agents and nucleotide analogs are "a chemically modified or altered form of" a dideoxynucleotide, they are considered to be dideoxynucleotide derivatives.

In the alternative, it would have been obvious to one skilled in the art at the time the invention was made to have used dideoxynucleotides, since dideoxynucleotides are nucleotide analogs and are used in the art interchangeably with the recitation of "nucleotide analogs" for

accomplishing the same function of terminating extension. See, for example, Hong et al. (USPN 5,747,928, col. 1, lines 35-63 and col. 5, lines 52-53), and Orgel et al. (USPN 4,865,968, col. 6, lines 63-64).

Stemmer also teaches the removal of nucleotides using polymerases having exonuclease activity (col. 9), the template can be any type of nucleic acid, nucleic acid analog or nucleic acid derivative, and the template and extended fragments can be various sizes (cols. 22-28).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Rosenthal (USPN 6,087,095, previously cited).

The teachings of Short are presented above. Specifically, Short teaches an in vitro recombination method using a defined primer, wherein at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative is added. Short teaches the at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative can be removed by heat (pg. 8). Short does not teach the modifying or removing of the at least one

dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative using an exonuclease.

However, Rosenthal teaches that if additional cycles of extension are to be performed, Exonuclease III can be added to remove a chain terminator (dideoxynucleotide) (col. 5-6).

In view of the teachings of Rosenthal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short so as to have removed the at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, in order to have achieved the benefit of providing additional cycles of nucleic acid extension for producing a plurality of polynucleotides that encode a polypeptide of interest.

Applicants' Arguments

Applicants' argue Short does not teach defined primers or adding at least one at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, and Rosenthal does not remedy the alleged deficiencies of Short, nor does Rosenthal present a motivation to combine (see pages 16-17 of Applicants' response).

Response to Applicants' Arguments

Applicants' arguments have been considered, but are not persuasive for the following reasons. First, Applicants' arguments with respect to the alleged deficiencies of Short is not persuasive for the reasons above (see Short 102(e) rejection and response to Applicants' Arguments therein). Furthermore, the motivation of Rosenthal (for teaching the use of Exonuclease for removing dideoxynucleotides (chain terminators) is presented above. Accordingly, the rejection is maintained.

10. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (USPN 6,506,603), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Rosenthal (USPN 6,087,095, previously cited).

The teachings of Stemmer are presented above. Specifically, Stemmer teaches an in vitro recombination method using a defined primer, wherein at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative is added. Stemmer teaches the chain terminating agent can be removed by a polymerase that has exonuclease activity. Stemmer does not teach the modifying or removing of the at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative using an exonuclease.

However, Rosenthal teaches that if additional cycles of extension are to be performed, Exonuclease III can be added to remove a chain terminator (dideoxynucleotide) (col. 5-6).

In view of the teachings of Rosenthal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Stemmer so as to have removed the at least one dideoxynucleotide, a dideoxynucleotide analog or a dideoxynucleotide derivative, in order to have achieved the benefit of providing additional cycles of nucleic acid extension for producing a plurality of polynucleotides that encode a polypeptide of interest.

11. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Fuller, C. (USPN 5,741,676).

The teachings of Short are presented above. Specifically, Short teaches an in vitro

recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Short does not teach adding alkaline phosphatase and exonuclease after adding the length-altering agent.

However, Fuller teaches the use of alkaline phosphatase and exonuclease, following an amplification reaction, is advantageous because it degrades undesirable primers and NTPs prior to further analysis (see abstract, col. 8, lines 15-29 and col. 9).

Accordingly, in view of the teachings of Fuller, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short so as to have added alkaline phosphatase and exonuclease, following the addition of a length-altering agent (i.e., following the end of an amplification reaction). One of ordinary skill in the art would have been motivated to modify the method of Short in order to have achieved the benefit of degrading undesirable primer and NTPs, enhancing further analysis.

12. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Volkov (USPN 6,534,292), as applied to claims 1-7, 9, 11-19, 21-41, 43-44, 46-47, 53-55 and 57 above, and in view of Fuller, C. (USPN 5,741,676).

The teachings of Volkov are presented above. Specifically, Volkov teaches an in vitro recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Volkov does not teach adding alkaline phosphatase and exonuclease after adding the length-altering agent.

However, Fuller teaches the use of alkaline phosphatase and exonuclease, following an amplification reaction, is advantageous because it degrades undesirable primers and NTPs prior to further analysis (see abstract, col. 8, lines 15-29 and col. 9).

Accordingly, in view of the teachings of Fuller, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Volkov so as to have added alkaline phosphatase and exonuclease, following the addition of a length-altering agent (i.e., following the end of an amplification reaction). One of ordinary skill in the art would have been motivated to modify the method of Volkov in order to have achieved the benefit of degrading undesirable primer and NTPs, enhancing further analysis.

13. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (USPN 6,506,603), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Fuller, C. (USPN 5,741,676).

The teachings of Stemmer are presented above. Specifically, Stemmer teaches an in vitro recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Stemmer does not teach adding alkaline phosphatase and exonuclease after adding the length-altering agent.

However, Fuller teaches the use of alkaline phosphatase and exonuclease, following an amplification reaction, is advantageous because it degrades undesirable primers and NTPs prior to further analysis (see abstract, col. 8, lines 15-29 and col. 9).

Accordingly, in view of the teachings of Fuller, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Stemmer so as to have added alkaline phosphatase and exonuclease, following the addition of a length-altering agent (i.e., following the end of an amplification reaction). One of ordinary skill in the art would have been motivated to modify the method of Stemmer in order to have achieved the benefit of degrading undesirable primer and NTPs, enhancing further analysis.

14. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Labeit et al. (DNA (1986) 5(2): 173-177, cited in the IDS).

The teachings of Short are presented above. Specifically, Short teaches an in vitro recombination method using a defined primer, wherein a nucleotide analog is incorporated into the extension product. Short does not teach nucleotide analog is a α-phosphorothioate nucleotide.

However, Labeit teaches using a α-phosphorothioate nucleotide is advantageous (in conjunction with Exonuclease III digestion) because it is less sensitive to previous methods, more efficient and "can yield reliable sequence information" (see pages 173 and 176).

Accordingly, in view of the teachings of Labeit, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short so as to have used a α-phosphorothioate nucleotide, in order to have achieved the benefit of providing a more efficient and more effective means of obtaining sequence information.

15. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Volkov (USPN 6,534,292), as applied to claims 1-7, 9, 11-19, 21-41, 43-44, 46-47, 53-55 and 57 above, and in view of Labeit et al. (DNA (1986) 5(2): 173-177, cited in the IDS).

The teachings of Volkov are presented above. Specifically, Volkov teaches an in vitro recombination method using a defined primer, wherein a nucleotide analog is incorporated into the extension product. Volkov does not teach nucleotide analog is a α-phosphorothioate nucleotide.

However, Labeit teaches using a α-phosphorothioate nucleotide is advantageous (in conjunction with Exonuclease III digestion) because it is less sensitive to previous methods, more efficient and "can yield reliable sequence information" (see pages 173 and 176).

Accordingly, in view of the teachings of Labeit, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Volkov so as to have used a α-phosphorothioate nucleotide, in order to have achieved the benefit of providing a more efficient and more effective means of obtaining sequence information.

16. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (USPN 6,506,603), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Labeit et al. (DNA (1986) 5(2): 173-177, cited in the IDS).

The teachings of Stemmer are presented above. Specifically, Stemmer teaches an in vitro recombination method using a defined primer, wherein a nucleotide analog is incorporated into the extension product. Stemmer does not teach nucleotide analog is a α-phosphorothioate nucleotide.

However, Labeit teaches using a α-phosphorothioate nucleotide is advantageous (in conjunction with Exonuclease III digestion) because it is less sensitive to previous methods, more efficient and "can yield reliable sequence information" (see pages 173 and 176).

Accordingly, in view of the teachings of Labeit, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Stemmer so as to have used a α-phosphorothioate nucleotide, in order to have achieved the benefit of providing a more efficient and more effective means of obtaining sequence information.

17. Claims 47-48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short et al. (WO 98/01581, cited in the IDS), as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Minami et al. (USPN 5,106,585).

The teachings of Short are presented above. Specifically, Short teaches an in vitro recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Short does not teach using the Maxam Gilbert chemical treatment.

However, Minami teaches the advantages of using the Maxam Gilbert treatment for creating fragments (see col. 1). Specifically, Minami states, "Maxam Gilbert is being widely used because it has the advantages of involving relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

Accordingly, in view of the teachings of Minami, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Short so as to have used the Maxam Gilbert chemical treatment for producing nucleic acid fragments. One of ordinary skill in the art would have been motivated to modify the method of Short in order to have achieved the benefits stated by Minami of providing "relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

18. Claims 48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volkov (USPN 6,534,292), as applied to claims 1-7, 9, 11-19, 21-41, 43-44, 46-47, 53-55 and 57 above, and further in view of Minami et al. (USPN 5,106,585).

The teachings of Volkov are presented above. Specifically, Volkov teaches an in vitro recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Volkov does not teach using the Maxam Gilbert chemical treatment.

However, Minami teaches the advantages of using the Maxam Gilbert treatment for creating fragments (see col. 1). Specifically, Minami states, "Maxam Gilbert is being widely used because it has the advantages of involving relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

Accordingly, in view of the teachings of Minami, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Volkov so as to have used the Maxam Gilbert chemical treatment for producing nucleic acid fragments. One of ordinary skill in the art would have been motivated to modify the method of Volkov in order to have achieved the benefits stated by Minami of providing "relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

19. Claims 47-48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. (USPN 6,506,603, as applied to claims 1-7, 9, 11-17, 19, 21-41, 43-44, 46, 53-55 and 57 above, and in view of Minami et al. (USPN 5,106,585).

The teachings of Stemmer are presented above. Specifically, Stemmer teaches an in vitro recombination method using a defined primer, wherein a length altering reagent is added to create fragments for producing a nucleic acid. Stemmer does not teach using the Maxam Gilbert chemical treatment.

However, Minami teaches the advantages of using the Maxam Gilbert treatment for creating fragments (see col. 1). Specifically, Minami states, "Maxam Gilbert is being widely used because it has the advantages of involving relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

Accordingly, in view of the teachings of Minami, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Stemmer so as to have used the Maxam Gilbert chemical treatment for producing nucleic acid fragments. One of ordinary skill in the art would have been motivated to modify the method of Stemmer in order to have achieved the benefits stated by Minami of providing "relatively simple experimental operations and comparing favorably in rapidity and accuracy with other determination procedures". See col. 1, lines 25-30.

Conclusion

20. No claims are allowable.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
February 23, 2004

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
2/23/2004